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(54) Title: THERAPEUTIC FOOD COMPOSITION AND METHOD TO DIMINISH BLOOD SUGAR FLUCTUATIONS

(57) Abstract

A therapeutic food composition for treatment of diabetic patients to diminish fluctuations in blood sugar levels and prevent hypoglycemic episodes, comprising per unit about 20-50 grams of nutrients including a slowly absorbed or digested complex carbohydrate, preferably cornstarch; a more rapidly absorbed complex carbohydrate; protein; and fat, but substantially no simple sugars. Diabetic patients may be treated to diminish blood sugar fluctuations and prevent hypoglycemia via the administration of the novel food composition as an evening or pre-bedtime snack or during the daytime hours to patients receiving insulin therapy or engaging in activities that might provoke hypoglycemia.

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THERAPEUTIC FOOD COMPOSITION AND METHOD TO DIMINISH BLOOD SUGAR FLUCTUATIONS

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of co-pending application Serial No. 08/213,542, filed March 15, 1994.

This invention relates to therapeutic treatments of diabetes mellitus. More particularly, this invention relates to treatment methods and compositions for the prevention of severe fluctuations in blood sugar levels in diabetic patients.

Symptoms of hypoglycemia fall into two main categories. Rapid epinephrine release causes sweating, tremor, tachycardia, anxiety, and hunger. Central nervous system symptoms include dizziness, headache, clouding of vision, blunted mental acuity, confusion, abnormal behavior, convulsions and loss of consciousness. When hypoglycemia is recurrent or severe, nervous system symptoms predominate, and the epinephrine phase may not be recognizable. With more rapid drops or wide swings in plasma glucose (as in insulin reactions), adrenergic symptoms are prominent (Harrison's Principles of Internal Medicine, 11th Ed., McGraw-Hill Book Company, New York, 1987, p. 1800).

Numerous strategies have been developed to achieve the goal of maintaining blood glucose at a relatively constant level in diabetic patients, such as open looped continuous subcutaneous insulin pumps and multiple daily injections of insulin. These intensive insulin regimens are coupled with home glucose monitoring, and many patients measure their blood glucose levels by finger prick up to 6 to 8 times per day to assure that close to normal blood sugar levels are maintained. This regimen is prescribed because studies have shown that by avoiding excessive high blood sugar levels, the long-term outcome of patients with diabetes can be improved. However, this regimen, which decreases episodes of high blood sugar, also causes patients to experience more low blood sugar reactions (hypoglycemia).

Results of the Diabetes Complication and Control Trial indicate that intensive insulin treatment, while it markedly delays and lessens long term retinal, nephrologic and

neuropathic disease, leads to a three to nine-fold increase in hypoglycemic events, most of which occur at night (L.Y. Dawson, Clinical Diabetes, 11:88-96, 1993). Sometimes these episodes of hypoglycemia are severe and can lead to loss of consciousness and convulsions. Severe hypoglycemic events seem to occur more often at night while the patient is asleep rather than during the day. When awake, diabetic patients can feel hypoglycemic reactions beginning, and can treat themselves with sugar in order to bring their blood sugar levels back into the normal range. When asleep, patients do not have this awareness, therefore the risk of hypoglycemia is much higher during this time.

The need exists to develop strategies to diminish hypoglycemia while continuing to intensively manage diabetes. Cornstarch has been used effectively to combat the hypoglycemia associated with glycogen storage disease type 1, a disease having an inherited absence or deficiency of glucose-6-phosphatase activity in the liver, kidneys, and intestines, leading to accumulation of glycogen in those organs and hypoglycemia during fasting. Protection against low blood sugar was provided for up to 6 to 8 hours after ingestion of uncooked cornstarch (J.I. Wolfsdorf, et al., Am. J. Clin. Nutr., 51:1051-7, 1990). However, the dosage of cornstarch used for this treatment was 1.75 grams per kilogram of body weight. This dosage is much higher than could be tolerated by a patient with diabetes mellitus.

Another study has also been conducted in patients with diabetes, giving cornstarch during inpatient hospitalization, with a reduction in the nadir of the blood glucose level. Children were fasted and then given the entire carbohydrate content of the standard bedtime snack (30 grams of carbohydrate) as uncooked cornstarch (M.T. Ververs, et al., Eur. J. Clin. Nutr., 47:268-73, 1983). However, in this study the cornstarch did little to prevent hypoglycemia and the researchers did not evaluate varying dosages to determine maximal efficacy.

Thus, the need exists for a better method of treating hypoglycemia in both Type I and Type II diabetics. In particular, a method of treatment or maintenance is required which will avoid serious hypoglycemic episodes while not provoking hyperglycemia.

Blood glucose levels in patients with diabetes mellitus are regulated and stabilized by ingesting a therapeutic food composition including a slowly metabolized complex

carbohydrate, preferably uncooked cornstarch, a more rapidly metabolized complex carbohydrate, protein and fat. The food composition is slowly absorbed from the gastrointestinal tract and maintains relatively stable blood sugar levels in the diabetic patient for up to nine hours.

The food composition, which may be in the form of a snack bar, is preferably administered to diabetic patients shortly before bedtime, and is effective in substantially preventing nocturnal episodes of hypoglycemia while not causing hyperglycemia.

The present invention pertains to a therapeutic food composition intended for administration to patients suffering from Type I or Type II diabetes to help maintain proper blood glucose regulation and prevent wide fluctuations therein, namely, hypoglycemic and hyperglycemic episodes. The therapeutic composition is to be administered as part of an overall program of treatment, including control of diet and the administration of insulin and/or other medications in appropriate cases.

The novel food composition comprises as its essential components:

a) a complex carbohydrate which is slowly absorbed from the human gastrointestinal tract (hereinafter "slowly absorbed carbohydrate"), i.e., is slowly digested and is not completely metabolized even after 3-4 hours;

b) a complex carbohydrate which is more rapidly absorbed from the digestive tract (hereinafter "rapidly absorbed carbohydrate");

c) protein; and

d) fat.

As used herein, the term "complex carbohydrates" refers to macromolecular carbohydrates including starches, polydextrose and other polysaccharides.

The therapeutic composition containing the foregoing components may be in any conventional "snack" form, e.g., bars, puddings, cookies, wafers, milkshakes and the like. Snack-type bars resembling candy or granola bars are most convenient for storage, handling and administration purposes and, when produced with scores, perforations or

grooves thereon, can be easily divided for purposes of administering a fraction of a bar where appropriate.

The novel food composition preferably contains about 20 to about 50 grams of nutrients per serving or unit, e.g., per bar, including:

- about 17-24 grams of total carbohydrates (about 5-15 grams of slowly absorbed carbohydrate and about 7-19 grams of rapidly absorbed carbohydrate);
- about 5-20 grams of protein; and
- about 3-7 grams of fat, preferably at least one-third monounsaturated fat.

The term "nutrients" as used herein refers to carbohydrates, proteins and fats.

The therapeutic food compositions of the invention preferably provides about 115-230 calories per serving or unit, of which:

- about 50-70% are from slowly absorbed and rapidly absorbed complex carbohydrates;
- about 15-25% are from protein; and
- about 15-25% are from fat.

In a preferred embodiment of the invention, the novel food composition is in the form of a bar including 17-24 grams of total carbohydrate, or the equivalent of one to one and one-half "bread exchanges" in a standard diabetic diet plan. The bar contains about 5-15 grams of slowly absorbed carbohydrate in the form of uncooked cornstarch, which generally comprises by weight about 27% amylose and 73% amylopectin. The preferred embodiment also contains about 7-19 grams of rapidly absorbed complex carbohydrate, but substantially no simple sugars; about 5-20 grams of protein; and about 3-7 grams of fat, at least one-third
as monounsaturated fat.

The ingredients in the therapeutic food composition may include any conventional food ingredients of adequate purity and wholesomeness which preferably supply the aforementioned amounts of total calories and percentage of calories from carbohydrates, protein and fat, respectively, and wherein the relative weight ranges of slowly absorbed

carbohydrates, rapidly absorbed carbohydrates, protein and fat are as indicated previously. In the preferred embodiment of a snack-type bar, the ingredients may include, by way of illustration, uncooked cornstarch as the slowly absorbed carbohydrate; polydextrose, peanuts, peanut derivatives (e.g., peanut butter), other nuts or nut derivatives as sources of rapidly absorbed carbohydrates, fat and protein; and other protein sources such as soy protein, whey protein, and casein hydrolysate. Artificial sweeteners or sugar substitutes (e.g., aspartame or sorbitol) may be included in the food composition, but no simple sugars such as sucrose. Coloring agents, water, salt, preservatives and other standard ingredients or additives normally used in the preparation of a snack or candy-type bar may be utilized as well, provided that the total nutrient and calorie profile of the finished bar or other form of the novel food composition comes within the parameters defined above.

Uncooked cornstarch is the preferred source of slowly absorbed carbohydrate for purposes of the invention since its carbohydrate content and its rate of metabolism are known and are relatively uniform, and it may be readily formulated into a variety of palatable food compositions.

Many diabetics routinely consume a bedtime snack containing about 30 grams of carbohydrate, often in the form of bread, cereal or milk. By the method of treatment of the present invention, patients suffering from diabetes mellitus are administered in place of, or as part of, their normal evening or pre-bedtime snack (in accordance with their recommended bread and protein exchanges) one to two servings or units of the therapeutic food composition, for example one to two bars prepared in accordance with the invention. The number of units administered, including fractions of a unit (such as half bars), will depend on the age, weight and condition of the patient, whether or not the patient takes insulin or other antidiabetic medication and the patient's nocturnal blood sugar profile as determined by finger stick blood glucose levels or other means of blood sugar management. The goal of the treatment is to prevent blood glucose levels from dropping below 60 mg/dl, defined as hypoglycemia, while not rising above 250 mg/dl, defined as hyperglycemia.

Dosage amounts of less than one unit may be utilized in younger pediatric patients or in patients who have demonstrated relatively little tendency towards nocturnal hypoglycemic events.

It has been found in clinical studies with diabetic children and adolescents that food compositions prepared in accordance with the invention and administered as described herein are effective in maintaining blood sugar levels in the "normal" range of 60 mg/dl - 250 mg/dl for as long as 8-9 hours or more after ingestion.

Patients taking insulin to facilitate post-prandial absorption of glucose can also be treated during the day with premeasured doses of the novel food composition, which will be slowly metabolized to the monosaccharide glucose over a period of six to eight hours, instead of receiving simple carbohydrates such as orange juice or other sugar sources that tend to cause a rapid peak in blood glucose level that quickly subsides. During waking hours the patient's use of, and hence requirement for, glucose is varied and depends upon the level and type of activity, e.g., vigorous exercise. The exact amount and frequency of the actual dose, therefore, will vary by patient and from day to day for each patient. A blood glucose test, usually administered as a finger stick to obtain a blood sample, can be used to monitor daily glucose levels as well as the patient's own subjective experience of symptoms associated with the onset of hypoglycemia. Therefore, in the practice of this invention sufficient complex carbohydrate is administered in the form of the novel food composition to maintain the blood glucose level somewhat above this level, nominally about 60 mg/dl in the average patient.

It will be appreciated by persons of skill in the medical arts generally and in the management of diabetic patients specifically that the composition and method of the present invention are valuable adjuncts to conventional diet management and drug or insulin therapy and can provide an easily administered and accepted modality to avoid excessive peaks and valleys in blood glucose levels, particularly the severe hypoglycemic episodes which are experienced by many diabetics.

The following are illustrative examples of the novel composition and method of the present invention. These examples are not intended, however, to provide ingredients,

specific formulations, methods of production or dosage regimens which must be utilized exclusively to practice the present invention.

EXAMPLE 1

Cornstarch-containing Bar

A therapeutic food composition was prepared in accordance with the invention in the form of a snack-type vanilla nut bar. The bar weighed a total of 31 g and contained sorbitol, cornstarch, soy protein isolate, peanut butter, water, polydextrose, peanuts, whey protein concentrate, natural flavors, lecithin and citric acid.

Nutritionally, the bar provided 120 calories (equivalent to one bread exchange), of which about 54% were from carbohydrates, 23% from protein and 23% from fat. The bar included 7 g of protein and about 3 g of total fat: about 0.5 g saturated fat, 1 g polyunsaturated fat and 1 g monounsaturated fat.

The total carbohydrate content of the bar was 17 g, of which 5 g were cornstarch (uncooked) and about 12 g were more rapidly absorbed carbohydrate provided primarily by the polydextrose and peanuts.

The bar contained 95 mg of sodium and 40 mg of potassium.

EXAMPLE 2

Treatment of Diabetic Patients

The bar of Example 1 was administered to eight diabetic children who had previously experienced episodes of nocturnal hypoglycemia. Each child consumed one bar as part of his or her regular evening snack for three to five consecutive nights, and the blood glucose levels of each patient were measured several times during the night and in the morning upon awakening.

As indicated by the data set forth in Table 1, only one patient exhibited hypoglycemia after consuming the therapeutic bar and only in one blood sugar reading out of well over a dozen taken from that patient, with hypoglycemia being defined as blood glucose levels <60 mg/dl. By contrast, the patients had all previously experienced

moderate to severe episodes of nocturnal hypoglycemia after consuming their regular evening snacks which did not contain cornstarch.

TABLE 1

Blood Glucose Readings (mg/dl)

Patient 1:

Day	1	2	3	4	5
0	68	340	188	221	172
1	65				
2	103	248	197	161	169
3	86				
4	116				
5	165	203	169	149	139
6	175				
7	204				
8	236	177	141	115	81

Patient 2:

Day	1	2	3	4
0	57	74	61	165
1		77		
2		64		
3	86	82	72	78
4		81		
5		77		
6	96	94	182	125
7		98		
8	80	82	172	163

Patient 3:

Day	1	2	3	4	5
0	144	51	219	256	101
1	201				
2	146	226	153	106	88
3	176				
4	96	101	180	87	93
5	74				
6	98	131	155	86	85
7	92				
8	114	211	279	114	142

Patient 4:

Day	1	2	3	4	5
0	160	144	88	96	144
1	102				
2	100	95	66	206	228
3					
4	97	50	83	265	146
5					
6	105				
7					
8	122	153	72	203	84

Patient 5:

Day	1	2	3	4	5
0	53	154	99	117	68
1	164	122	138	199	85
2	128	157	148	194	103
3	146	158	175	175	86
4	124	156	122	124	116
5	116	157	131	140	165
6	102	156	105	139	175
7	108	160	107	132	204
8	118	167	110	149	285

Patient 6:

Day	1	2	3
0	52	129	212
1			
2			
3	106	83	188
4			
5			
6	97	132	
7			
8	124	175	179

Patient 7:

Day	1	2	3	4
0	134	78	67	242
1				
2				
3				
4				
5				
6	177	115	132	
7				
8	196	132	169	205

Patient 8:

Day	1	2	3
0	320	160	365
1			
2	269	327	264
3			
4			
5			
6	282	387	228
7			
8	175	322	223

The unique formulation of the novel food composition, blending slowly and rapidly absorbed carbohydrates, protein and fat, allows for the gradual hydrolysis and absorption of the complex carbohydrates and maintains the blood sugar level stable for up to eight to nine hours, diminishing hypoglycemia in diabetic subjects after the post-prandial period.

It has thus been shown that there are provided compositions and methods which achieve the various objects of the invention and which are well adapted to meet the conditions of practical use.

As various possible embodiments might be made of the above invention, and as various changes might be made in the embodiments set forth above, it is to be understood that all matters herein described are to be interpreted as illustrative and not in a limiting sense.

What is claimed as new and desired to be protected by Letters Patent is set forth in the following claims.

I CLAIM:

1. A therapeutic food composition for treatment of diabetic patients to diminish fluctuations in blood sugar levels and prevent hypoglycemic episodes, comprising per serving or unit about 20-50 grams of nutrients, including:

a) about 5-15 g of slowly absorbed complex carbohydrate;

b) about 7-19 g of rapidly absorbed complex carbohydrate;

c) about 5-20 g of protein; and

d) about 3-7 g of fat.

2. A composition according to claim 1 with a total carbohydrate content of about 17-24 g.

3. A composition according to claim 1 wherein said slowly absorbed carbohydrate is cornstarch.

4. A composition according to claim 3 wherein said cornstarch is uncooked.

5. A composition according to claim 3 which comprises about 5g of cornstarch per unit.

6. A composition according to claim 1 wherein at least one-third of said fat is monounsaturated fat.

7. A therapeutic food composition for treatment of diabetic patients to diminish fluctuations in blood sugar levels and prevent hypoglycemic episodes, said composition providing per serving or unit about 115-230 calories of which:

a) about 50-70% are from slowly absorbed and rapidly absorbed complex carbohydrates;

b) about 15-25% are from protein; and

c) about 15-20% are from fat.

8. A composition according to claims 1 or 7 in the form of a snack bar, pudding, cookie, wafer or milkshake.

9. A composition according to claim 8 in the form of a snack bar.

10. A composition according to claim 9 wherein said bar is produced with scores, perforations or grooves thereon for easy division into fractions of a unit.

11. A composition according to claims 1 or 7 which is substantially free of simple sugars.

12. A composition according to claims 1 or 7 wherein said rapidly absorbed carbohydrates, protein and fat are provided by polydextrose, peanuts, peanut derivatives or other nuts or nut derivatives.

13. A composition according to claim 1 or 7 wherein said protein is provided by soy protein, whey protein or casein hydrolysate.

14. A method of treating a diabetic patient to diminish fluctuations in blood sugar levels and prevent hypoglycemic episodes, said method consisting of the administration to the patient of a therapeutic food composition comprising per serving or unit about 20-50 grams of nutrients including:

a) slowly absorbed complex carbohydrate;

b) rapidly absorbed complex carbohydrate;

c) protein; and

d) fat.

15. A method according to claim 14 wherein said composition comprises per unit:

a) about 5-15 g of slowly absorbed carbohydrate;

b) about 7-19 g of rapidly absorbed carbohydrate;

c) about 5-20 g of protein; and

d) about 3-7 g of fat.

16. A method according to claim 15 wherein said composition comprises per unit about 17-24 g of total carbohydrates.

17. A method according to claim 14 wherein said slowly absorbed carbohydrate is cornstarch.

18. A method according to claim 17 wherein said cornstarch is uncooked.

19. A method according to claim 17 wherein said composition comprises about 5 g of cornstarch per unit.

20. A method according to claim 14 wherein at least one-third of said fat is monounsaturated.

21. A method according to claim 14 wherein said composition is in the form of a snack bar, pudding, cookie, wafer or milkshake.

22. A method according to claim 21 wherein said composition is in the form of a snack bar.

23. A method according to claim 22 wherein said bar is produced with scores, perforations or grooves thereon for easy division into fractions of a unit.

24. A method according to claim 14 wherein about 1-2 units of said composition are administered to the patient.

25. A method according to claim 14 wherein one half unit of said composition is administered to the patient.

26. A method according to claim 14 wherein said composition is administered to the patient as an evening or pre-bedtime snack.

27. A method according to claim 14 wherein said composition is administered during the daytime to a patient receiving insulin therapy or engaging in exercise.

28. A method according to claim 14 wherein said patient is a child or adolescent.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/10803

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A23L1/29 A23L1/09 A23L1/0522 A23L1/305 A23L1/30
A61K31/715

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,5 169 662 (A.SPICER) 8 December 1992 see column 1, line 36-37 see column 1, line 48-56 see column 3, line 10-22 see column 4, line 10-22 see column 5, line 17-23 see column 6, line 6-14 see column 7, line 31-44 see column 8, line 31-43 see claims 1,11 ---	1-13
A	EP,A,0 504 055 (ROUSSEL-UCLAF) 16 September 1992 see page 2, line 36 see page 3, line 5-6 see page 4, line 54-55; claims; examples --- -/--	1-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
18 July 1996	26.07.96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	**Authorized officer** Van Moer, A

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 443 789 (MATSUTANI) 28 August 1991 see page 1, line 45-52; claims	1-13
A	CLINICAL DIABETES, vol. 11, no. 4, August 1993, ALEXANDRIA,VA., pages 88-96, XP002008753 L.Y.DAWSON: "DCCT and Primary Care:Prescription for Change" cited in the application see the whole document	1-13
A	AMERICAN JOURNAL OF CLINICAL NUTRITION, vol. 52, 1990, pages 1051-1057, XP002008754 J.I.WOLFSDORF ET AL.: "Physical growth and development of children with type 1 glycogen-storage disease:comparison of the effects of long-term use of dextrose and uncooked cornstarch" cited in the application see the whole document	1-13
A	EUROPEAN JOURNAL OF CLINICAL NUTRITION, vol. 47, 1993, LONDON, pages 268-273, XP002008755 M.T.C.VERVERS ET AL.: "Complex carbohydrates in the prevention of nocturnal hypoglycemia in dibateic children" cited in the application see the whole document	1-13

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INTERNATIONAL SEARCH REPORT

Information on patent family members

L ational Application No
PCT/US 95/10803

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-5169662	08-12-92	NONE		
EP-A-504055	16-09-92	FR-A-	2673812	18-09-92
		AT-T-	128606	15-10-95
		CA-A-	2062920	14-09-92
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		DE-T-	69110496	09-11-95
		ES-T-	2044796	16-01-94
		US-A-	5344824	06-09-94

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/10803

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 14-28: Rule 39.1 (iv)

Claims searched completely: 1-13, Claims searched incompletely: None
Claims not searched 14-28

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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